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Abstract: Assessment of the effect of clonidine on depth of anaesthesia is difficult because clonidine combines analgesic, sedative and direct haemodynamic effects. We thus evaluated the influence of clonidine on the bispectral index (BIS) and its potential dose-sparing effect on propofol. After induction of anaesthesia with target-controlled infusion of propofol and obtaining an unchanged bispectral index (pre-BIS), clonidine 4 microg kg⁻¹ or placebo was administered randomly to 50 patients in a double-blind manner. Subsequently, if there was a decrease in BIS we reduced the target concentration of propofol until pre-BIS was reached. The pre-BIS was maintained and a remifentanyl infusion was added during surgery. The courses of the BIS, heart rate and blood pressure were recorded and the total amounts of intra-operative propofol and remifentanyl were determined. Assessment of implicit memory during anaesthesia was performed with an auditory implicit memory test consisting of item sequences. Administration of clonidine resulted in a decrease in the BIS from 45 (SD 4) to 40 (6) ($P < 0.001$), which allowed a reduction of propofol target concentration from 3.3 (0.6) to 2.7 (0.7) microg ml⁻¹ ($P < 0.001$) and measured propofol concentration from 2.9 (0.6) to 2.5 (0.7) kg ml⁻¹ ($P = 0.009$) in order to maintain the pre-BIS value. During subsequent surgery, propofol requirements were reduced by 20% ($P = 0.002$) in the clonidine group and a similar amount of remifentanyl was used in each group. The increase in anaesthetic depth given by clonidine can therefore be measured with bispectral EEG analysis and allows reduction of the propofol dose to achieve a specific depth of anaesthesia.

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Clonidine decreases propofol requirements during anaesthesia: effect on bispectral index

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Assessment of the effect of clonidine on depth of anaesthesia is difficult because clonidine combines analgesic, sedative and direct haemodynamic effects. We thus evaluated the influence of clonidine on the bispectral index (BIS) and its potential dose-sparing effect on propofol. After induction of anaesthesia with target-controlled infusion of propofol and obtaining an unchanged bispectral index (pre-BIS), clonidine $4 \mu\text{g kg}^{-1}$ or placebo was administered randomly to 50 patients in a double-blind manner. Subsequently, if there was a decrease in BIS we reduced the target concentration of propofol until pre-BIS was reached. The pre-BIS was maintained and a remifentanyl infusion was added during surgery. The courses of the BIS, heart rate and blood pressure were recorded and the total amounts of intra-operative propofol and remifentanyl were determined. Assessment of implicit memory during anaesthesia was performed with an auditory implicit memory test consisting of item sequences. Administration of clonidine resulted in a decrease in the BIS from 45 (SD 4) to 40 (6) ($P < 0.001$), which allowed a reduction of propofol target concentration from 3.3 (0.6) to 2.7 (0.7) $\mu\text{g ml}^{-1}$ ($P < 0.001$) and measured propofol concentration from 2.9 (0.6) to 2.5 (0.7) $\mu\text{g ml}^{-1}$ ($P = 0.009$) in order to maintain the pre-BIS value. During subsequent surgery, propofol requirements were reduced by 20% ($P = 0.002$) in the clonidine group and a similar amount of remifentanyl was used in each group. The increase in anaesthetic depth given by clonidine can therefore be measured with bispectral EEG analysis and allows reduction of the propofol dose to achieve a specific depth of anaesthesia.

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Clonidine, a centrally acting α_2 -receptor agonist, has attracted increasing interest as an adjunct to anaesthesia. A variety of beneficial effects before, during and after anaesthesia, such as sedation, analgesia, increased cardiovascular stability and improved outcome, have been attributed to clonidine.^{1,2} Clonidine reduced the requirement for volatile anaesthetics when assessed by haemodynamic responses.^{3,4} Imai found that a reduced dosage of propofol was required after administration of clonidine,⁵ whereas Goyagi found a reduced induction but not maintenance dose of propofol when using haemodynamic end-points.⁶ However, assessing anaesthetic depth by the use of haemodynamic variables after administration of clonidine,

which depresses autonomic nervous system responses, is fraught with difficulties. A lack of tachycardia or hypertension does not necessarily indicate an adequate depth of anaesthesia. Because centrally acting α_2 -receptor agonists have effects on the EEG and the bispectral index (BIS) in the awake patient, we thought that the effect of clonidine on depth of anaesthesia might also be monitored using the BIS.^{7,8} This study was conducted to evaluate first whether the sedative effect of clonidine is measurable by BIS analysis during propofol anaesthesia, and secondly whether BIS monitoring allows the maintenance of a constant anaesthetic depth despite a reduced propofol dosage after administration of clonidine.

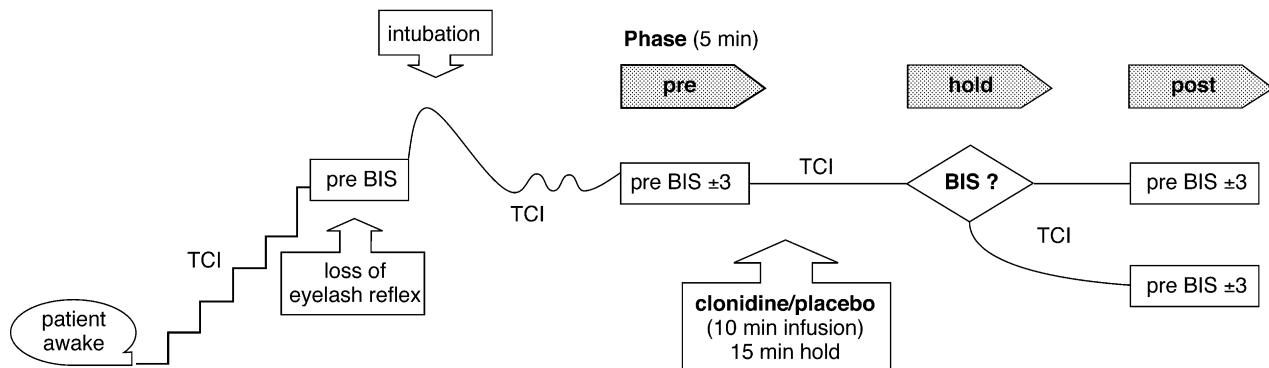


Fig 1 Study design: preoperative examination. BIS?: after clonidine/placebo infusion, the BIS response was evaluated. With an unchanged BIS the target plasma concentration of propofol (TCI) was maintained; when a decrease in the BIS was observed, the target plasma concentration of propofol was reduced until the BIS was again at the pre-BIS level.

Materials and methods

This randomized, double-blind, placebo-controlled study was designed to test the hypothesis that clonidine deepens anaesthesia as measured by the BIS and allows the dose of propofol to be reduced.

After obtaining institutional review board approval and written informed consent, we studied 50 German-speaking patients, aged 18–70 yr, American Society of Anesthesiologists physical status I or II, scheduled for superficial surgical procedures expected to last at least 45 min. Patients with cardiopulmonary, neuropsychiatric or hearing disorders and patients taking any medication affecting cardiovascular or neurological function were excluded. Patients received no premedication.

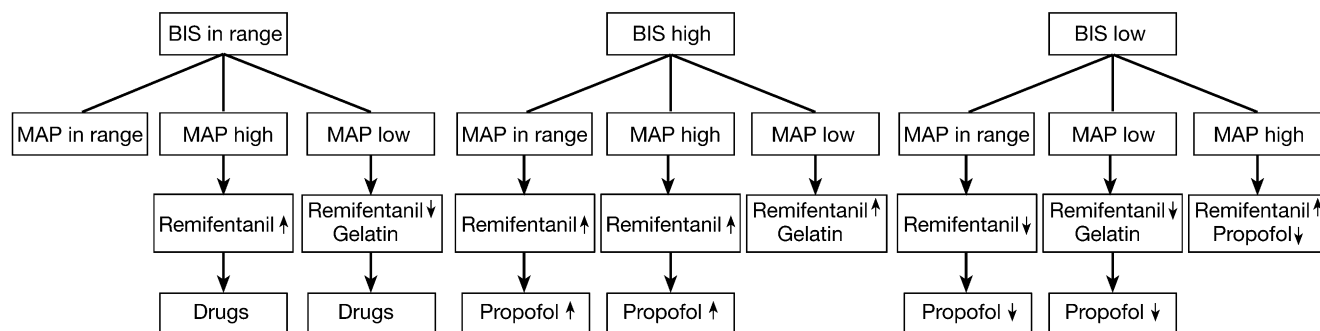
After admission of the patients to the operating room, an i.v. cannula was placed and standard monitoring was established. In addition, the level of consciousness was surveyed by bispectral EEG analysis (Aspect A-1000 EEG monitor, software module 3.12; Aspect Medical Systems, Natick, MA, USA) and expressed as the BIS. After preparation of the skin, four disposable, self-prepping, low-impedance electrodes (Zipprep; Aspect Medical Systems) were positioned over the left and right prefrontal cortex (Fp1, Fp2) and referenced to a central vertex electrode (Cz) according to a standard montage. Impedances were kept at less than 5000 Ω .

Anaesthesia was induced by propofol infusion using a target-controlled infusion (TCI) pump (Graseby 3500; Graseby Medical, Watford, UK). The target plasma concentration of propofol ($\mu\text{g ml}^{-1}$) was raised in incremental steps until the patient became unconscious, as defined by the loss of the eyelash reflex. The corresponding BIS was recorded. To intubate the trachea, anaesthesia was deepened by increasing the target plasma concentration of propofol and muscle paralysis was achieved with rocuronium 0.6 mg kg^{-1} . During the whole procedure, the patients' lungs were ventilated with 40% oxygen in air. The target plasma concentration of propofol was adjusted to achieve a

constant level of anaesthesia, indicated by a BIS corresponding to the BIS at loss of eyelash reflex (pre-BIS). The target concentration of propofol was adjusted in steps of 0.1–0.5 $\mu\text{g ml}^{-1}$. A steady state was assumed only when the calculated effect site concentration equalled the target plasma concentration.

Keeping the propofol target concentration constant, we allocated the patients randomly to receive either an infusion of clonidine 4 $\mu\text{g kg}^{-1}$ or placebo in 0.9% NaCl 100 ml during the following 10 min. If the BIS was altered 15 min after the end of infusion, the target plasma concentration of propofol was reduced until the pre-BIS value was reached (Fig. 1). Heart rate, arterial blood pressure, the BIS and target plasma concentration of propofol were recorded every 2 min. Blood samples for measuring the blood concentration of propofol were taken via an additionally established 14 G cannula in a large vein on the contralateral arm before ('pre' phase) and 15 min after clonidine or placebo infusion ('hold' phase) and after adjusting the propofol target concentration ('post' phase), to achieve a steady state, defined as a constant BIS ($= \text{pre-BIS} \pm 3$) over a period of at least 5 min. The blood samples (4 ml heparinized tubes) were stored immediately at -20°C and analysed by high-performance liquid chromatography with fluorescence detection.⁹

During the surgery, supplementary analgesia was provided by remifentanyl infusion at a rate between 0.01 and 1 $\mu\text{g kg}^{-1} \text{ min}^{-1}$ to maintain an unchanged BIS and haemodynamic stability (Fig. 2). The target concentration of propofol was maintained unchanged unless the target BIS ($\text{pre-BIS} \pm 5$) could not be maintained by varying the remifentanyl infusion rate, and at the end of the operation to allow a fast wake-up. Heart rate, arterial blood pressure, BIS, propofol target concentration and remifentanyl infusion rate were recorded every 5 min during the intra-operative course. Hypertension or hypotension ($\pm 20\%$ of the arterial blood pressure in the 'pre' phase) occurring with the BIS in the target range or sudden and marked blood pressure changes were scheduled to be treated with esmolol (20 mg)

**Definitions**BIS in range: pre BIS \pm 5

MAP high: > 120 mm Hg or pre MAP + > 20%

MAP low: < 50 mm Hg or pre MAP - > 20%

Tachycardia: > 120 beats min^{-1} Bradycardia: < 40 beats min^{-1} **Dosage**Propofol: 1.5–8 $\mu\text{g ml}^{-1}$ Remifentanyl: 0.01–1 $\mu\text{g kg}^{-1} \text{min}^{-1}$ **Treatment of acute haemodynamic events**

MAP high: Esmolol 20 mg or Phentolamine 1 mg i.v.

MAP low: Ephedrine 5 mg i.v.

Tachycardia: Esmolol 20mg i.v.

Bradycardia: Atropine 0.5 mg i.v.

Fig 2 Anaesthetic decision tree during the operation.

or phentolamine (1 mg) respectively, ephedrine (5 mg) and gelatin (500 ml). Simultaneously, remifentanyl and propofol dosing was adjusted in accordance with the study protocol (Fig. 2). Atropine (0.5 mg) was administered if the heart rate fell below 40 beats min^{-1} . Plasma concentrations of clonidine were analysed from blood samples 15 min ('hold' phase) and 180 min after clonidine infusion and at the end of surgery. Heparinized blood (6 ml) was placed on ice immediately after sampling, centrifuged promptly at +4°C to separate the plasma, and stored at -20°C until analysis by high-performance liquid chromatography. To avoid clonidine redosing, the propofol-sparing efficacy was assessed during the first 180 min after clonidine administration.

To assess implicit memory during anaesthesia, four test items of different categories were presented to the patients through headphones at the following time points: immediately before ('pre' phase), 15 min after ('hold' phase), after possible reduction of propofol ('post' phase) and 180 min after infusion of clonidine (or the end of the operation, whichever came first). The test items were selected in a pilot study in which 48 patients were asked to name 10 items from four categories (animals, fruits, colours, countries). The sequence in which these items were named was recorded and we evaluated which item was named on average in 10th position. These four items, named last in each category, were selected to be presented to the patients in the present study. On the post-operative day, patients in the current study were asked to name 10 items in each category. The sequence in which these items were named was again recorded. Scores of test items (10 points for first position, 9 points for second position, .. and 0 points for not mentioning the item at all) were computed for each study time point (pre, hold,

post and intra-operative) to compare the clonidine and placebo groups.¹⁰ Explicit memory was assessed by asking for any free recall.

Statistical analysis

The duration of the different phases of the intra-operative course and memory test items were analysed using the Mann-Whitney *U*-test and Fisher's exact test. Repeated measures analysis of variance with two within-group factors [phase (pre, hold, post) and repetition (steady state values in each phase)] and one between-group factor (clonidine/placebo) and *post hoc t*-test with Bonferroni correction were performed to evaluate differences in the progression of the preoperative phases pre, hold and post. To analyse differences between phases (pre, hold post) within groups (clonidine, placebo), paired *t*-tests with Bonferroni correction were used. Continuous data are presented as mean (SD). *P* values less than 0.05 were considered significant.

Results

The two groups were similar with regard to the physical characteristics of the patients (Table 1) and the type of operation. Times from the end of the preoperative examination to the start of the operation and the duration of operation did not differ between the groups (Table 1).

Pre-operative measurements before and after administration of clonidine

TCI values, BIS, measured propofol blood concentrations, heart rate and mean arterial blood pressure were similar in the two groups before starting the clonidine or placebo infusion in the 'pre' phase (Fig. 3). Fifteen minutes after the infusion (hold phase), haemodynamic variables were still

Table 1 Patient characteristics and operative times. Values are mean (SD) or absolute count. Op. time=duration of operation; SO time=time from end of pre-operative study phase to start of operation; Ext. time=time from end of operation to extubation

	Clonidine (n=25)	Placebo (n=25)
Age (yr)	38 (20–62)	39 (18–65)
Males	10	13
Weight (kg)	69 (13)	75 (14)
Height (m)	1.69 (0.11)	1.71 (0.07)
ASA I	22/25	22/25
ASA II	3/25	3/25
Op. time (min)	130 (70)	138 (83)
SO time (min)	40 (36)	46 (27)
Ext. time (min)	5 (7)	3 (5)

similar between the groups but there was a significant decrease in heart rate in both groups ($P<0.001$). In the 'hold' phase, the BIS showed a significant decrease in the clonidine group ($P<0.001$) and was significantly lower than in the placebo group ($P=0.002$). After achieving pre-BIS in the 'post' phase, the clonidine group showed a significant decrease in the target propofol concentration ($P<0.001$) and measured blood concentrations of propofol ($P=0.009$), and a significant decrease in heart rate and mean arterial pressure (MAP) ($P=0.002$). In the 'post' phase, the target propofol concentration ($P=0.002$) and the measured propofol blood concentrations ($P=0.006$) were significantly lower in the clonidine group than in the placebo group, but similar BIS values ($P=0.403$) (Fig. 3) resulted. The measured plasma concentrations of clonidine were in the therapeutic range ['hold' phase, 2.7 (0.8) ng ml⁻¹; 180 min after clonidine administration or the end of operation, 1.7 (0.5) ng ml⁻¹].

Intra-operative measurements

Throughout the intra-operative course, similar values for the BIS were observed in the two groups. In the clonidine group, this was achieved despite lower propofol target concentrations and a reduced total propofol dosage (Table 2). Interestingly, patients in both groups received similar amounts of remifentanyl (Table 2). Despite a significant decrease in mean intra-operative MAP, the patients in the clonidine group needed similar amounts of gelatin, atropine and ephedrine (Table 2). No patient was treated with phentolamine or esmolol. The time to extubation did not differ between the groups (Table 1).

Implicit and explicit memory analysis

There were no differences in age or gender between patients in the pilot study and those in the current study [mean age: pilot group 38 (18–75) yr; current group 38 (18–65) yr; male/female 20/28 vs 23/27]. The scores for the presented items were similar between the pilot study and the current study and between the clonidine and the placebo groups at

all time points ($P>0.05$) (Fig. 4). No patient had any free recall either of the presented items or of any other pre- or intra-operative events.

Discussion

Intravenous clonidine results in a decrease in the BIS during propofol anaesthesia and allows reduction of the target concentration of propofol in order to maintain a certain BIS level. The pharmacodynamic effect of clonidine during anaesthesia can thus be monitored with the BIS.

Clonidine affects the EEG in a variety of ways: it increases slow-wave activity (delta) and attenuates the physiological alpha fluctuations.^{7–11} Although no data exist regarding the specific effect of clonidine on the BIS, clonidine causes sedation¹² and therefore may also affect the BIS,¹³ which indeed was demonstrated in the present study.

The propofol saving in the current study of nearly 20% is comparable with earlier studies in which an isoflurane saving of approximately 40% was reported.^{14–15} The somewhat greater isoflurane saving in that study may be explained by a different EEG analysis, a larger dose of clonidine (5 vs 4 µg kg⁻¹) and perhaps especially because isoflurane dosing was guided mainly by haemodynamic responses. Another trial investigated the effect of clonidine on i.v. anaesthesia with propofol and fentanyl and found a reduction of approximately 40% in the propofol requirement with similar doses of fentanyl after clonidine.⁵ Despite similar anaesthetics and a relatively small dose of oral clonidine (150 µg), this study revealed a greater reduction of propofol in comparison with our study. This may be explained by dosing propofol according to arterial blood pressure and heart rate but without any monitoring of brain function, such as the BIS.

Larger doses of clonidine may allow greater reductions in anaesthetic drug use, but may lengthen the time required for recovery from anaesthesia.⁶ This was not observed in the present study and the time to extubation was similarly short in the two groups. The restrictive propofol dosing in our control group may be another reason for the relatively small propofol saving compared with previous studies. This might be linked to continuous monitoring of the BIS, which has been reported to facilitate immediate recovery and to decrease the consumption of anaesthetics.¹⁶

Clonidine administration resulted in a lower propofol requirement for a certain level of anaesthesia to be achieved, as defined by similar BIS values. The fact that no explicit intra-operative awareness occurred and no signs of implicit memory were observed indicates that the anaesthetic state induced by clonidine and low-dose propofol may be similar to the anaesthetic state induced by a larger dose of propofol alone. It is evident that larger trials will be necessary to show conclusively that a lower dose of propofol combined with clonidine is as safe as a larger dose propofol in preventing intra-operative awareness.

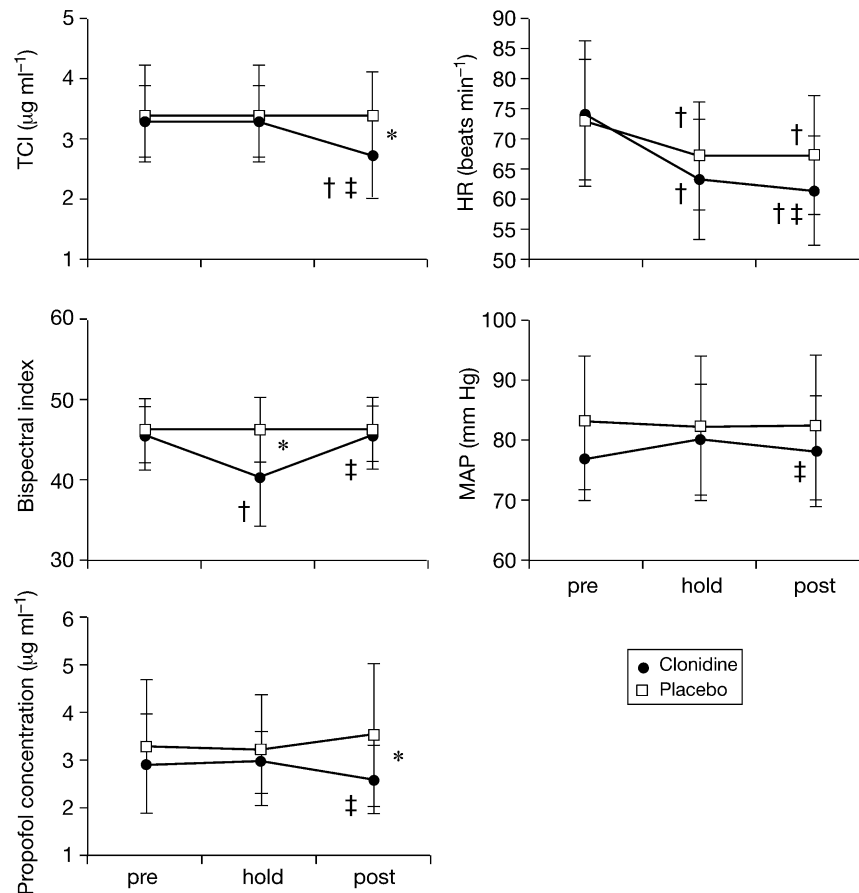


Fig 3 Propofol target plasma concentration (TCI), bispectral index, blood concentration of propofol, heart rate (HR) and mean arterial pressure (MAP) before (pre) and after (hold) clonidine administration and after achieving the pre-BIS-value (post) with possible reduction of propofol in patients treated with i.v. clonidine or placebo (mean±SD). †Significant difference from 'pre' condition (within-group comparison, after Bonferroni correction, $P<0.017$). ‡Significant difference from 'hold' condition (within-group comparison, after Bonferroni correction, $P<0.017$). *Significant difference between groups (after Bonferroni correction, $P<0.017$).

Table 2 Intra-operative BIS, haemodynamic variables, anaesthetic requirements and the use and dose of gelatin, atropine and ephedrine for haemodynamic events. Values are mean (SD), absolute counts or median and range. BIS=bispectral index; HR=heart rate; MAP=mean arterial pressure; Prop=intra-operative propofol infusion rate; Remi=intra-operative remifentanyl infusion rate. $P<0.05$ is significant

	Clonidine	Placebo	<i>P</i> (clonidine vs placebo)
BIS	48 (4)	48 (4)	0.73
HR (beats min ⁻¹)	53 (5)	54 (7)	0.46
MAP (mm Hg)	71 (7)	78 (9)	0.01
Target concentration of propofol (µg ml ⁻¹)	2.3 (0.4)	2.8 (0.5)	<0.01
Prop (mg kg ⁻¹ min ⁻¹)	0.11 (0.02)	0.13 (0.02)	<0.01
Remi (µg kg ⁻¹ min ⁻¹)	0.14 (0.08)	0.11 (0.08)	0.13
Use of gelatin	10/25	10/25	1
Gelatin (ml)	0 (0–1500)	0 (0–1000)	0.48
Use of atropine	5/25	4/25	0.73
Atropine (mg)	0 (0–1.5)	0 (0–1.0)	0.67
Use of ephedrine	4/25	1/25	0.35
Ephedrine (mg)	0 (0–10)	0 (0/5)	0.16

We analysed the propofol concentration of venous blood to avoid the insertion of an arterial catheter or repeated arterial puncture. In addition, we ensured that the time to steady state was always more than 10 min,

and thus arterial and venous propofol concentrations should have been stable and in a fixed ratio to each other.¹⁷ Therefore, venous propofol concentrations may be considered representative of the blood concentration

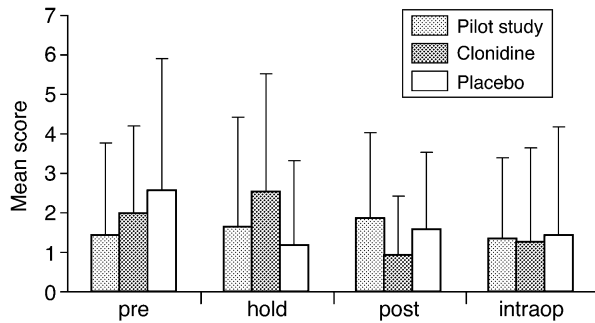


Fig 4 Scores of test items (10 = first position, 1 = 10th position, 0 = not listed) at different time points in the current study (clonidine vs placebo) and in the pilot study. There are no significant differences between the groups. Values are mean+SD.

of propofol when comparing different phases and the two groups.

Clonidine did not have any additional effect in reducing the intra-operative requirement for remifentanyl. This is in agreement with a study by Engelman and colleagues, describing similar intra-operative opioid requirements with and without clonidine.¹⁸ However, clonidine has been reported to reduce post-operative opioid requirements.¹⁹ Because the primary site of analgesic action of clonidine has been proposed to be the spinal dorsal horn, it is conceivable that systemically administered clonidine has a relatively limited analgesic efficacy, enabling modulation of post-operative pain but being less effective against the more intense intra-operative pain.²⁰

In summary, the pharmacodynamic effect of i.v. clonidine can be monitored with the BIS. Intravenous clonidine causes a significant decrease in the BIS and allows a lower propofol dose to be used at a similar level of anaesthesia without intra-operative awareness or prolonged recovery times.

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